

WHAT IS CLAIMED IS:

1. A method for inducing tolerance in a mammal to a pre-selected antigen comprising the steps of

a. isolating peripheral blood mononuclear cells (PBMC) from a whole blood sample from said mammal;

b. isolating dendritic cells from said PBMC;

c. exposing said dendritic cells *ex vivo* to apoptotic cells expressing said pre-selected antigen in the presence of at least one dendritic cell maturation stimulatory molecule and in the absence of effective CD4⁺ T cell help;

d. introducing a cellular portion of step c) into said mammal;

wherein said dendritic cells induce apoptosis of antigen-specific CD8⁺ T cells in said mammal resulting in tolerance to said antigen.

2. The method of claim 1 wherein said dendritic cell maturation stimulatory molecule is PGE₂, TNF- α , lipopolysaccharide, monocyte conditioned medium, CpG-DNA, or any combination thereof.

- 1 3. The method of claim 1 wherein said absence of effective CD4+ T cell is achieved by
2 excluding CD4+ T cells from said step c).
3
- 4 4. The method of claim 1 wherein said absence of effective CD4+ T cell help is achieved by
5 including in step c) at least one agent that inhibits or eliminates effective CD4+ T cell
6 help.
7
- 8 5. The method of claim 4 wherein said agent which inhibits or eliminates effective CD4+
9 help is a monoclonal antibody to a TNF superfamily member, a combination thereof, a
10 monoclonal antibody to a receptor for a TNF superfamily member, or a combination
11 thereof
12
- 13 6. The method of claim 5 wherein said TNF superfamily member is CD40L, TRANCE,
14 OX40 or DR3.
15
- 16 7. The method of claim 5 wherein said receptor for a TNF superfamily member is CD40,
17 TRANCE, OX40 ligand or TWEAK.
18
- 19 8. The method of claim 1 wherein said absence of effective CD4+ T cell is achieved by
20 inhibiting formation of mature forms of MHC II / peptide complexes within the dendritic
21 cell.
22

- 1 9. The method of claim 8 wherein said inhibiting is achieved by preventing cleavage of
2 invariant chain.
3
- 4 10. The method of claim 9 wherein said preventing is achieved by addition of a cathepsin
5 inhibitors.
6
- 7 11. The method of claim 8 wherein said inhibiting is achieved by blocking loading of
8 peptides by inhibiting HLA-DM.
9
- 10 12. The method of claim 8 wherein said inhibiting is achieved by preventing successful
11 antigen degradation and formation of a MHC II peptide epitope.
12
- 13 13. The method of claim 12 wherein said preventing is achieved by inhibiting cathepsin D or
14 alternative proteases.
15
- 16 14. The method of claim 8 wherein said inhibiting is achieved by inhibiting transport of
17 MHC II / peptide complexes to the cells surface.
18
- 19 15. The method of claim 4 wherein said agent which inhibits or eliminates effective CD4 T
20 cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.
21
- 22 16. The method of claim 15 wherein said agent is selected from a FKBP antagonist and a
23 TOR antagonist.

- 1 17. The method of claim 16 wherein said FKBP antagonist is FK-506.
- 2
- 3 18. The method of claim 16 wherein said TOR antagonist is rapamycin.
- 4
- 5 19. The method of claim 1 wherein said pre-selected antigen is a tumor antigen, a viral
- 6 antigen, a self antigen or a transplant antigen.
- 7
- 8 20. The method of claim 4 wherein said presence of at least one agent that inhibits effective
- 9 CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.
- 10
- 11 21. The method of claim 1 wherein after a period of time following step c), a cellular portion
- 12 is infused into the mammal.
- 13
- 14 22. The method of claim 1 wherein said mammal is a human.
- 15
- 16 23. A method for inducing tolerance in a mammal to a pre-selected antigen comprising the
- 17 steps of
- 18 a. providing a dendritic cell chemoattractant at a site in a mammalian body, said
- 19 site comprising an antigen to which tolerization of an immune response is desired or
- 20 made to comprise an antigen to which tolerization of an immune response is desired
- 21 by administration of said antigen to said site; and
- 22

b. administering to said site or systemically to said mammal an agent which inhibits or eliminates effective CD4⁺ T cell help;

wherein immune system cells of said mammal are tolerized to said antigen.

24. The method of claim 23 wherein said dendritic cell chemoattractant is a ligand for CCR6.

25. The method of claim 23 wherein said ligand for CCR6 is 6-C-kine.

26. The method of claim 23 wherein said agent which inhibits or eliminates effective CD4⁺ help is a monoclonal antibody to a TNF superfamily member, a combination thereof, a monoclonal antibody to a receptor for a TNF superfamily member, or a combination thereof.

27. The method of claim 26 wherein said TNF superfamily member is CD40L, TRANCE, OX40 or DR3.

28. The method of claim 26 wherein said receptor for a TNF superfamily member is CD40, TRANCE, OX40 ligand or TWEAK.

1 29. The method of claim 23 wherein said agent which inhibits or eliminates effective
2 CD4+ T cell inhibits formation of mature forms of MHC II / peptide complexes within the
3 dendritic cell.

4
5 30. The method of claim 29 wherein said inhibits formation is achieved by preventing
6 cleavage of invariant chain.

7
8 31. The method of claim 29 wherein said inhibits or eliminates is achieved by addition of
9 a cathepsin inhibitor.

10
11 32. The method of claim 29 wherein said inhibiting is achieved by blocking loading of
12 peptides by inhibiting HLA-DM.

13
14 33. The method of claim 32 wherein said inhibiting is achieved by preventing successful
15 antigen degradation and formation of a MHC II peptide epitope.

16
17 34. The method of claim 33 wherein said preventing is achieved by inhibiting cathepsin
18 D or alternative proteases.

19
20 35. The method of claim 29 wherein said inhibiting is achieved by inhibiting transport of
21 MHC II / peptide complexes to the cells surface.

36. The method of claim 23 wherein said agent which inhibits or eliminates effective CD4 T cell help inhibits signalling consequent to dendritic cell-CD4 T cell engagement.

37. The method of claim 36 wherein said agent is selected from a FKBP antagonist and a TOR antagonist.

38. The method of claim 37 wherein said FKBP antagonist is FK-506.

39. The method of claim 37 wherein said TOR antagonist is rapamycin.

40. The method of claim 23 wherein said pre-selected antigen is a tumor antigen, a viral antigen, a self antigen or a transplant antigen.

41. The method of claim 23 wherein said presence of at least one agent that inhibits effective CD4 T cell help comprises a monoclonal antibody to TRANCE and FK-506.